REMARKS

Claims 1-11 are pending in the present application. Claims 1-11 have been amended herein.

Claim Rejections–35 U.S.C. § 102

Claim 1 was rejected under 35 U.S.C. § 102 (b) as being anticipated by Van Berkel ("Derivatization for Electrospray Ionization Mass Spectrometry. 3. Electrochemical Ionizable Derivatives," Anal. Chem. 1998, **70** 1544-1554). The Van Berkel reference has been cited by the Office for disclosing an improvement of analysis of compounds with electrospray ionization mass spectrometry (ES-MS) by derivatizing analytes, e.g., stigmasterol and pinacol with ferrocenyl boronate esters. The Office further concludes that the Van Berkel reference demonstrates ferroceneboronate derivatives of stigmasterol and pinacol "will be much easier to oxidize than most organic species found in a typical ES system. Moreover, once oxidized in the ES capillary, the derivative radical cations should be sufficiently stable to survive in solution until sprayed." Applicant respectfully traverses this argument.

Claim 1 has been amended to claim the characterization of the structure of a carbohydrate - rather than characterization of a chemical compound- by electrospray tandem mass spectrometry by derivatization with ferrocenyl boronate. It is Applicant's position that the present invention is not anticipated by Van Berkel. To successfully present a case for anticipation under § 102, the Office must show that each element of the claim in issue is found, either expressly or under principles of inherency, in a single prior art reference, or that the claimed invention was previously known or embodied in a single prior art device or practice. See Apple Computer, Inc. v. Articulate Systems, Inc., 234 F.3d 14 (Fed. Cir. 2000). The Office admits that "Van Berkel does not disclose using

ferrocenboronate derivatives specifically for carbohydrates..." See Office Action, page 3. In the Van Berkel reference, the main derivative is ferrocenecarbamate ester. While Van Berkel uses an electrospray quadrupole ion trap mass spectrometer and ferrocene boronic acid for a derivative, Van Berkel does not teach this method for carbohydrates. Therefore, this reference cannot form the basis for an anticipation rejection under § 102. Applicant therefore requests that this rejection be withdrawn.

Claim Rejections–35 U.S.C. § 103

Claims 2-3 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Van Berkel in view of Yang et al. ("Stereochemical effects in mass spectrometry (VII)" Chem. Res. Chin. Univ. 1991, **8** 231-238) and Desaire et al. ("Differentiation of Diastereomeric N-Acetylhexosamine Monosaccharides Using Ion Trap Tandem Mass Spectrometry." Anal. Chem. 1999, **71** 1997-2002). The Office admits that the Van Berkel reference does not disclose "using ferroceneboronate derivatives specifically for carbohydrates." But the Office cites the Yang reference as disclosing "the advantages of using boronic derivatives, including areneboronates of various monosaccharides and disaccharides for their stereospecific determination by fast atom bombardment mass spectrometry (FAB MS), because boron compounds react stereoselectively with two hydroxyl groups of the saccharides." Based on this interpretation of the Yang reference, the Office argues that it would have been obvious for one of ordinary skill in the art to apply Van Berkel's method to saccharides, because "Yang demonstrates efficiency of using areneboronic derivatives of saccharides for FAB mass spectrometric analysis, and ES-MS is a more advanced and modern technique of mass spectrometry, for which advantages of using specific boronic compounds, namely ferrocenboronates, are demonstrated by Berkel

[*sic*]." Applicant respectfully traverses this rejection because the Office has failed to meet its burden for determining obviousness under 35 U.S.C. § 103 (a).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. But the fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. See In re Mills, 916 F.2d 680 (Fed. Cir. 1990).

In this case, the prior art does not suggest the desirability of the combination of the Van Berkel reference and the Yang reference to produce the claimed invention. More importantly, the Office has failed to explain why one of ordinary skill in the art at the time of the claimed invention would have been motivated to make the proposed modification to arrive at the claimed invention.

The Office argues that it would have been obvious to modify the reference to apply Van Berkel's method to saccharides, "because Yang demonstrates efficiency of using areneboronic derivatives of saccharides for FAB mass spectrometric analysis, and ES-MS is a more advanced and modern technique of mass spectrometry, for which advantages of using specific boronic compounds, namely ferroceneboronates, are demonstrated by Van Berkel." See Office Action, page 3. But the proper analysis is to ask why one would be

motivated to apply this application. There must be some suggestion or motivation either in the references themselves or in the knowledge generally available to one of ordinary skill in the art to modify the reference. In other words, the Van Berkel and Yang references must provide the motivation or suggestion to apply the Van Berkel method to saccharides because Yang demonstrates efficiency of such a method. Simply put, the Van Berkel and Yang references fail to suggest or motivate one of ordinary skill in the art to modify the references to apply Van Berkel's method to saccharides because of efficiency indicated in the Yang reference. The Van Berkel reference discloses "derivatives to enhance ES-MS analysis of simple alcohols, sterols, and phenols." See Van Berkel, page 1544. Most importantly, nowhere is there any suggestion to use electrospray tandem mass spectrometry for carbohydrates. Because no such suggestion exists, claims 2-3 are patentable over Van Berkel and Yang. Accordingly, Applicant requests that the rejection be withdrawn.

The Office points to the Desaire reference as demonstrating the importance of stereospecific detection of various N-acetylated hexose carbohydrates and concludes that claim 2-3 are unpatentable over Van Berkel in view of Yang et al. and Desaire et al. The Office maintains that it would have been obvious for one of ordinary skill in the art to apply Van Berkel's method to Yang's method to N-acetylated hexose carbohydrates- as seen in the Desaire reference- because N-acetylated hexose carbohydrates are a specific group of saccharides possessing OH-groups which stereospecifically react with boron compounds. Applicant respectfully disagrees.

The Desaire reference discloses derivatization of hexosamines with Co III-DAP (Cobalt III-diaminopropane). The Desaire reference derivative binds the nitrogen of the N-acetyl group and one of the hexose -hydroxyl oxygens to provide an enhanced molecular ion signal in positive electrospray -quadrupole ion trap mass spectrometry.

Applicant's ferrocenyl boronate derivative works well with carbohydrates. In fact, Applicant's derivative provides molecular ions that on fragmentation yield definitive structural information on monosaccharides and disaccharides including linkage information. Certainly there is no disclosure or even a suggestion of combining the method employed by Van Berkel and Yang to N-acetylated hexose carbohydrates as disclosed in Desaire. The Desaire reference fails to correct the deficiencies of the Van Berkel reference as well as the Yang reference. Accordingly, Applicant asks that the rejection be withdrawn.

Claims 4-6 and 10-11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Van Berkel in view of Yang. The Office recognizes that Van Berkel "does not teach using ferroceneboronate derivatives of specifically saccharides listed in claims 4-6 and 10-11, for ES-MS analysis." However, the Yang reference is cited as disclosing negative ion FAB mass spectrometry of saccharides, including those recited in claims 4-6 and 10-11, using areneboronic acid which stereospecifically reacts with mono- and disaccharides. Therefore, the Office presumes it would have been obvious for one skilled in the art to apply Van Berkel's method to saccharides of claims 4-6 and 10-11, because the Yang reference demonstrates efficiency of using areneboronic derivatives for FAB mass spectrometric analysis.

Once again, Applicant argues that to make out a case for obviousness under 35 U.S.C. §103(a), the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination. See Hodosh v. Block Drug Co., Inc., 786 F.2d 1136, 1143 n.5 (Fed. Cir. 1996). Even if the combination of the references taught every element of the claimed invention, without a motivation to combine, a rejection based on obviousness is improper. See In re Rouffet, 149 F.3d 1350, 1357 (Fed. Cir. 1998). In this case, there is no motivation to combine the Yang reference

and the Van Berkel reference. The Van Berkel reference and the Yang reference do not suggest the desirability and obviousness of extending the Van Berkel method to saccharides because Yang demonstrates efficiency of using areneboronic derivatives for FAB mass spectrometric analysis.

The Yang reference discloses the application of negative ion FAB ionization to observe carbohydrates. FAB produces singly charged molecular ions from analytes entrained in liquid matrix on a probe surface. Sector mass spectrometry is usually used to observe the ions species produced. The Yang reference does not disclose the utilization of electrospray tandem mass spectrometry. Electrospray tandem mass spectrometry produces multiply charged molecular ions from the sprayed solution phase. The ferrocene boronic acid derivative permits sensitive characterization of monosaccharides and disaccharides sprayed into the orifice of a quadrupole ion trap mass spectrometer in positive mode. This technique is ideal for interfacing HPLC separation utilizing post-column derivatization to the front of a mass spectrometer. Quadrupole ion trap or triple quadrupole MS are most often employed in this function. Sector instrumentation is not easily interfaced with HPLC separation under any circumstance. FAB cannot directly interface to an HPLC separation, by its very nature. Therefore, Applicant respectfully requests the withdrawal of this rejection.

Claim Objections

Claims 7-9 were objected to as being dependent upon a rejected base claim, but according to the Office, would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The claims have been amended to overcome this objection. Applicant respectfully requests the withdrawal of this objection and allow the claims as amended.

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AUG 29 2003
PATENT & TRADEMARK OFFICE

CONCLUSION

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

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